

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.

1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE November 1997	3. REPORT TYPE AND DATES COVERED Unknown	
4. TITLE AND SUBTITLE There is no difference in the incidence of postoperative nausea and vomiting (PONV) when ondansetron (ZOFTRAN) is administered prior to induction of emergence from general anesthesia			5. FUNDING NUMBERS	
6. AUTHOR(S) CPT Catherine Peuterbaugh CPT Bradley West				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Unknown			8. PERFORMING ORGANIZATION REPORT NUMBER HSC-SN00-000	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) Unknown			10. SPONSORING / MONITORING AGENCY REPORT NUMBER NA-1997-04	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release; Distribution is unlimited				
13. ABSTRACT (Maximum 200 words) The purpose of this study was to determine if ondansetron is more effective in the prevention of PONV when administered prior to induction versus prior to emergence from general endotracheal anesthesia. This was a prospective, randomized, double-blind study of ASA I-III patients. Group I received ondansetron at induction (n=75) and Group II received ondansetron at emergence (n=75). A general anesthesia protocol was followed and data was collected in the recovery room and at 24 hours. Group I had a 28.1% incidence of nausea in the PACU and 1.2 hours of nausea for the 24 hours post emergence, while Group II had a 23.4% incidence in the PACU and 1.5 hours respectively. Vomiting in the PACU for the Group I was 4.8% and 25% at 24 hours post emergence. Group II had a 1.6% incidence of vomiting in the PACU and 14% at 24 hours. No significant difference was found between these two groups of mostly of female patients. When ondansetron 4 mg IV is administered at induction or emergence from general endotracheal anesthesia, patients experience a similar incidence of PONV in the recovery room and up to 24 hours post emergence.				
14. SUBJECT TERMS Postoperative Nausea and Vomiting, Ondansetron, General Anesthesia			15. NUMBER OF PAGES 100	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT UNCLASSIFIED	18. SECURITY CLASSIFICATION OF THIS PAGE UNCLASSIFIED	19. SECURITY CLASSIFICATION OF ABSTRACT UNCLASSIFIED	20. LIMITATION OF ABSTRACT UL	

20041008 305

THERE IS NO DIFFERENCE IN THE INCIDENCE OF POSTOPERATIVE
NAUSEA AND VOMITING (PONV) WHEN ONDANSETRON (ZOFTRAN)
IS ADMINISTERED PRIOR TO INDUCTION OR EMERGENCE
FROM GENERAL ANESTHESIA.

DISTRIBUTION STATEMENT A
Approved for Public Release
Distribution Unlimited

By

Catherine Peuterbaugh, CPT, BSN, MSA

Bradley West, CPT, BSN

A Cluster Research Study
submitted in partial fulfillment
of the requirements for the degree of
Master of Science in Nursing
The University of Texas Health Science Center at Houston
School of Nursing
November, 1997

ABSTRACT

THERE IS NO DIFFERENCE IN THE INCIDENCE OF POSTOPERATIVE
NAUSEA AND VOMITING (PONV) WHEN ONDANSETRON
(ZOFTRAN) IS ADMINISTERED PRIOR TO
INDUCTION OR EMERGENCE FROM
GENERAL ANESTHESIA.

Introduction

The purpose of this study was to determine if ondansetron is more effective in the prevention of PONV when administered prior to induction versus prior to emergence from general endotracheal anesthesia.

Methods

This was a prospective, randomized, double-blind study of 150 ASA I-III patients. Group I received ondansetron at induction ($n = 75$) and Group II received ondansetron at emergence ($n = 75$). A general anesthesia protocol was followed and data was collected in the recovery room and at 24 hours.

Results

Group I had a 28.1 % incidence of nausea in the PACU and 1.2 hours of nausea for the 24 hours post emergence, while Group II had a 23.4% incidence in the PACU and 1.5 hours respectively. Vomiting in the PACU for the Group I was 4.8% and 25% at 24 hours post emergence. Group II had a

1.6% incidence of vomiting in the PACU and 14% at 24 hours. No significant difference was found between these two groups of mostly of female patients.

Conclusion

When ondansetron 4 mg IV is administered at induction or emergence from general endotracheal anesthesia, patients experience a similar incidence of PONV in the recovery room and up to 24 hours post emergence.

TABLE OF CONTENTS

	Page
ABSTRACT.....	ii
THESIS SIGNATURE SHEET.....	vi
WRAMC LETTER OF APPROVAL.....	vii
ACKNOWLEDGEMENTS.....	viii
LIST OF TABLES.....	ix
LIST OF FIGURES.....	x
 CHAPTER	
I Introduction.....	1
Statement of the Problem.....	4
Conceptual Framework.....	4
Purpose.....	9
Definition of Terms.....	9
Research Hypothesis.....	10
Significance of the Problem.....	10
Assumptions.....	13
Limitations.....	13
Summary.....	14
II Review of Related Literature.....	15
Summary.....	28
III Methodology.....	30
Population, Sample, and Setting.....	30
Instrumentation.....	34
Procedure for Data Collection.....	35
Protection of Human Subjects.....	36
Study Design.....	37
Procedure for Data Analysis.....	37
Summary.....	39
IV Analysis of the Data.....	40

Findings.....	52
Summary.....	58

	Page
V Discussion, Conclusions, Implications, and Recommendations.....	60
Discussion.....	60
Conclusion.....	66
Implications for Nursing Practice.....	66
Recommendations for Future Research.....	67

APPENDICES

A Letter of Permission for Figure.....	70
B Script for Data Collection by Recovery Room Nurses/Second Stage Recovery Staff.....	71
C Ondansetron Study Data Sheet	72
D Script for Obtaining 24 Hour Post-Emergence Data.....	74
E Script for Obtaining Consent.....	76
F Induction Sequence.....	78
G Script for Training Recovery Room/Second Stage Recovery/Same Day Surgery Staff in Data Collection Process.....	81
REFERENCES.....	83
VITAE.....	89

THERE IS NO DIFFERENCE IN THE INCIDENCE OF POSTOPERATIVE NAUSEA
AND VOMITING (PONV) WHEN ONDANSETRON (ZOFTRAN) IS ADMINISTERED
PRIOR TO INDUCTION OR EMERGENCE FROM
GENERAL ANESTHESIA.

By

Catherine Peuterbaugh, CPT, BSN, MSA

Bradley West, CPT, BSN

APPROVED:

Timothy Newcomer, MAJ, PhD., Chairperson

Rebecca K. LaChance, DNS, MS

Donald T. Albee Jr., MAJ, MHS



REPLY TO
ATTENTION OF:
MCHL-CI(40-38a)

DEPARTMENT OF THE ARMY
WALTER REED ARMY MEDICAL CENTER
WASHINGTON, DC 20307-5001

3 January 1997

MEMORANDUM FOR CPT Catherine Peuterbaugh, AN, Anesthesia Nursing Program,
Department of Nursing, Walter Reed Army Medical Center,
Washington, DC 20307-5001

SUBJECT: Approval to Begin Protocol WU# 7557: Administration of Ondansetron at Induction
or Emergence: Is There a Difference in Postoperative Nausea and Vomiting?

1. Your protocol was approved by the Clinical Investigation Committee (CIC) on 19 November 1996, and by the Human Use Committee (HUC) on 26 November 1996 as a "greater than minimal risk" human use protocol and has been assigned Work Unit #7557. Required revisions were received on 20 December 1996. A copy of the minutes from the applicable committee(s) is attached for your file. Also, enclosed is the approved consent form that must be duplicated and used for enrolling subjects. You may begin work on the project upon receipt of this letter.
2. Funding in the amount of \$1,500 (\$1,000 for travel and \$500 for reprints) was approved. All DCI funding is contingent on the availability of funds in the DCI budget and the adherence to applicable spending guidelines and policies. If your study was approved for acceptance of loaned equipment or the provision of an investigational drug/placebo, investigational device, supplies, contract services, and/or gift of money or property, you must coordinate this requirement with Ms. Charlene Thomas, Chief, Research Administration Service, DCI, Building #6, Room 4012, (202) 782-7102. Only the Pharmacy Service, not the principal investigator, is authorized to receive and dispense drugs.
3. Significant or unexpected side effects must be reported to the Medical Monitor of this study, LTC John Chiles, MC, Staff Anesthesiologist, Anesthesia-Operative Service, Department of Surgery.
4. As the principal investigator, you are required by WRAMC 70-1 and other Federal regulations to submit the following in a timely fashion to the Department of Clinical Investigation: (a) addenda delineating any changes in the protocol, (b) notification of significant or unexpected side effects, and (c) annual progress reports. Also enclosed is a copy of the WRAMC Multiple Project Assurance that all investigators agree to adhere to in conducting research, as attested to by your submission of a signed Principal Investigator Responsibilities Statement.
5. If you have any questions, please feel free to contact me or Ms. Walden at (202) 782-7861.

4 Encls
as

MICHAEL A. CAROME
MAJ, MC

Co-Chairperson, Human Use Committee

LIST OF TABLES

Table	Page
1 Demographic Characteristics of the Induction and Emergence Groups (Age and BMI).....	42
2 Demographic Characteristics of the Induction and Emergence Groups (Race, Sex, and History of PONV).....	44
3 Percentage Comparison of Independent Cofactors for the Induction and Emergence Groups.....	48

LIST OF FIGURES

Figure	Page
1 Vomiting Center.....	6
2 Comparison of the Amounts of Medications in the Induction and Emergence Groups.....	50
3 The Incidence of Nausea in the 24 hour Post Emergence period.....	55

CHAPTER I

Introduction

Despite the technologic advances in the practice of anesthesia, the search for effective postoperative management of associated complications such as nausea and vomiting continues. Postoperative nausea and vomiting (PONV) is a common complication of surgery (Rust & Cohen, 1994). Not only is PONV an unpleasant experience for patients, it may be associated with increased cost to the patient and the hospital. The associated mental, physical, and monetary problems caused by PONV warrants further research in the area of prevention and a reassessment of current therapies.

PONV is unpleasant and costly for the patient. In a study by Lee and Hirsch (1992), patients ($n=121$) were surveyed concerning the effects of PONV on their mental and physical well-being. Fifty-four percent ($n=65$) of the patients experiencing PONV described limitations on physical activities, concentration, appetite, and sleep. According to a study by Orkin (1992), PONV was the primary postoperative concern of 40% ($n=19$) of the patients. The subjects in this study who chose PONV as their primary postoperative concern were willing to accept a variety of

trade-offs (dysphoria, decreased mental acuity, increased pain, increased costs) in order to avoid nausea and vomiting. According to Sanchez and Hirsch (1992), patients may experience indirect costs such as lost wages due to missed work and lost wages of family members who may miss work caring for a patient at home.

The prevention of PONV is important in order to decrease the costs of hospitalization (Hirsch, 1994). PONV can increase the costs of hospitalization by increasing the time spent in the recovery room along with a concomitant increase in staffing requirements, drugs, and supplies. For every additional 2 hours spent in the recovery room due to PONV, one surgical case is delayed, resulting in nonproductive operating room time (Hirsch, 1994). PONV is the most common cause of unplanned hospital admission for outpatient surgical procedures (Hirsch, 1994). Preventing PONV could shorten hospital stays and could also conserve hospital resources and increase productivity in the operating room (Sanchez & Hirsch, 1992).

Common therapies utilized for the treatment of PONV include a variety of medications, such as droperidol and metoclopramide. These drugs, however, are associated with several side effects which are unpleasant for patients. The side effects include abnormal involuntary movements,

alterations in muscle tone, and postural disturbances (Du Pen et al., 1992; Melnick, 1988; Shavari et al., 1992).

New developments in the treatment of PONV are often brought about by borrowing knowledge and medications from other related medical patient populations. Ondansetron (Zofran), an antiemetic with few side effects, has commonly been used for cancer patients undergoing chemotherapy treatment. When ondansetron is compared to a placebo, 76 % (n=103) of the patients were emesis-free compared to the placebo at 46% (n=64) (ondansetron package insert, 1995). Its use in the prevention and treatment of PONV is relatively new and optimal administration times have yet to be determined (Dupeyron et al., 1993; Rust & Cohen, 1994).

The basis for the timing of administration of ondansetron is related to its pharmacokinetic profile. The onset of IV ondansetron is immediate, the peak effect is variable, and the duration is 12-24 hours. The elimination half-life for ondansetron is approximately 3.5 to 5.5 hours in adults (ondansetron package insert, 1995). Because of the relatively short half-life, it may be reasonable to administer it near the end of the surgical procedure, especially for those longer than 2 hours duration (Joslyn, 1994).

Statement of the Problem

This study addressed the timing of ondansetron administration to determine if there was a difference in the incidence of PONV when ondansetron was administered at induction compared to when ondansetron was administered at emergence from general anesthesia.

Conceptual Framework

This study was guided by a conceptual physiologic model of nausea and vomiting. This framework addresses the influences that contribute to nausea and vomiting. There are many nervous tissues within the body that are associated with causing nausea and vomiting when stimulated. The vomiting center is the core of this framework and is influenced directly and indirectly by higher centers in the brain, the chemoreceptor trigger zone (CTZ), emetics, antiemetics, and a variety of mechanical and chemical receptors (Berne & Levy, 1993). This model provides a conceptual framework for the interaction of emetic stimuli and antiemetic medications. The original model was adapted with permission from the author (see Appendix A) to incorporate antiemetic medications into the model. The model was further simplified by categorizing receptors by class, either chemical or mechanical. This model provides a

simplistic way in which to conceptualize a variety of complex interactions.

In the last twenty years scientists have identified an area within the central nervous system known as the "vomiting center" (see Figure 1) which is located in the medulla (Berne & Levy, 1993). The vomiting center is influenced indirectly by higher centers within the cerebral cortex via their modulatory influence on the CTZ. The CTZ is directly influenced by emetics which are chemical substances that trigger vomiting (i.e. general anesthetics, opioids, cholinomimetics, dopaminergics) and is also influenced by antiemetics (i.e. ondansetron, droperidol, metoclopramide) (Hirsch, 1994). The CTZ is located in the area postrema on the blood side of the blood brain barrier which is located on the floor of the fourth ventricle. Because of this location, it is easily accessed by chemicals in the blood (Berne & Levy, 1993; Goodman Gillman, 1996).

The vomiting center is also directly influenced by a variety of mechanical and chemical receptors. The labyrinthine receptors are central mechanical receptors in the middle ear that can be stimulated by movement, thereby activating the vomiting center. Peripheral mechanical receptors, such as touch receptors in the throat, can be

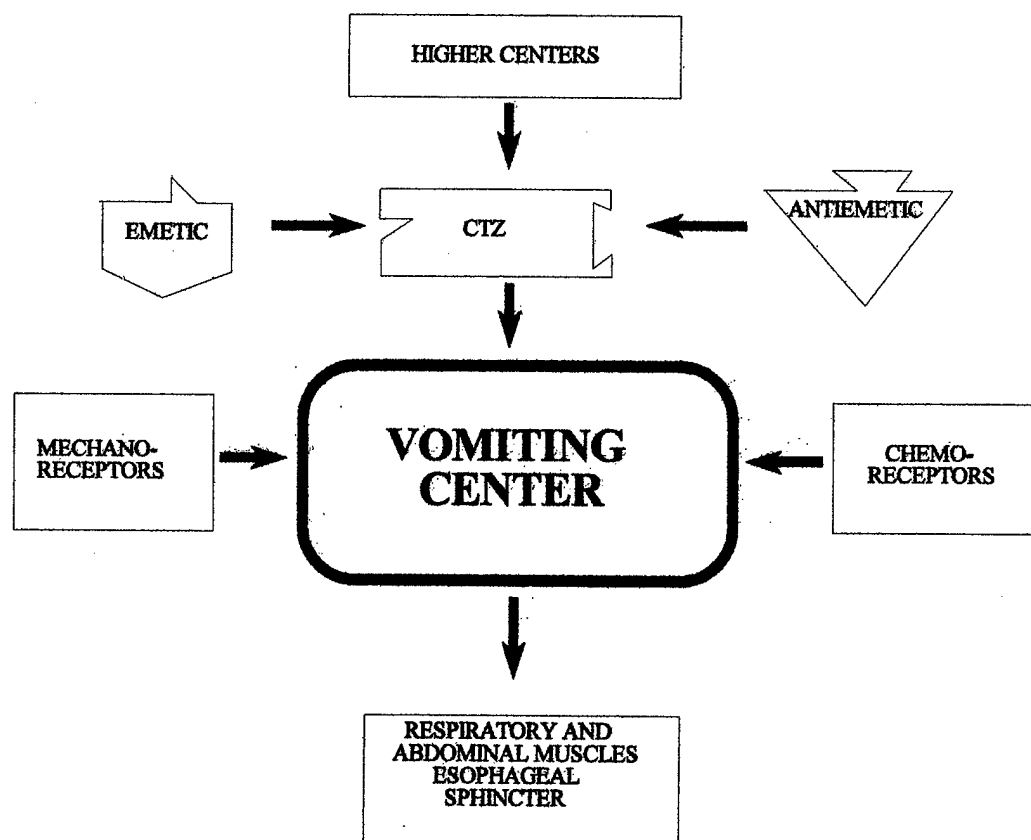


Figure 1. The vomiting center located in the medulla and various inputs and outputs

Adapted from: Physiology (p. 640) by R. M. Berne and M. N. Levy, 1993, St. Louis: Mosby Year Book Inc. Adapted with permission of author.

stimulated by suctioning, intubation, and oral surgery. Certain surgical procedures are associated with the stimulation of mechanoreceptors in various parts of the body which can interact with the vomiting center. These procedures include intra-abdominal surgery, major gynecologic surgery, laparoscopic surgery, orthopedic surgery, and ear, nose, and throat surgery (Kenny, 1994). In addition to the chemoreceptors located on the CTZ, there are chemoreceptors located in the periphery. An example of a chemoreceptor found in the periphery is the type found in the stomach and duodenum, which can be stimulated by the presence of blood or nitrous oxide.

When the areas that influence the vomiting center are stimulated, they activate the vomiting center to send efferent impulses to the respiratory and abdominal muscles, as well as to the esophageal sphincter, causing vomiting (Berne & Levy, 1993). Currently, there are no treatments to prevent the stimulation of mechanoreceptors and touch receptors, however, there are a variety of medications which act as antagonists for emetic agents on chemoreceptors (Joslyn, 1994). Ondansetron, a newer drug used in the treatment of PONV, acts as an antagonist for emetics which act upon the CTZ via a specific class of serotonin receptor, the 5-hydroxytryptamine subtype 3 (5HT3) receptor. The 5HT

subtype 3 receptor is a ligand gated ion channel that causes the depolarization of the neuron via increased conductance of Na^+ and K^+ . Ondansetron blocks the opening of this ion channel and thus depolarization, which prevents subsequent development of nausea and vomiting. 5HT₃ receptors are located centrally in the CTZ as well as peripherally within the body (Naylor & Inall, 1994). Ondansetron also acts on peripheral 5HT₃ receptors located on vagal afferent terminals which innervate the gastrointestinal mucosa. These peripheral and central chemoreceptors are stimulated by the release of serotonin (5HT) in response to cytotoxic agents and physical disruption of cells due to surgical manipulation (Naylor & Inall, 1994). Serotonin release has been shown to be a common pathway in the mediation of PONV (Naylor & Inall, 1994). It is theorized that anesthetic agents themselves may have a central effect on the emetic reflex via this common pathway of serotonin release (Naylor & Inall, 1994). The Clarke classical theory of receptors states that for a drug to exert its effects it must occupy the receptor (Goodman Gillman, 1996). Once an antagonist (ondansetron) occupies the receptor it takes more agonist (serotonin) to overcome the antagonists effect and the reverse is also true (Goodman & Gillman, 1996). Although much is known about the mechanism of action of ondansetron,

little information has been elucidated on the effectiveness of administration related to timing.

Purpose

The purpose of this study was to determine if ondansetron was more effective in decreasing PONV when administered prior to the induction of general anesthesia versus administration at emergence.

Definition of Terms

Emergence

Conceptual Definition: the time following the administration and termination of general anesthesia when the patient exhibits increased awareness, response to stimuli, and return of sympathetic tone (Foster & Jordan, 1994)

Operational definition: approximately 15 minutes prior to the removal of the endotracheal tube

Induction

Conceptual definition: identified by a rapid loss of consciousness leading to a light surgical plane of anesthesia following the administration of an IV sedative hypnotic (Miller, 1994)

Operational definition: period beginning with giving the patient propofol.

Nausea

Conceptual definition: the patient's conscious recognition of subconscious excitation in the area of the medulla, closely associated with or part of the vomiting center (Guyton, 1994)

Operational definition : in the PACU, a positive response to the question, "Do you feel sick to your stomach?"; after discharge from the PACU, a verbal numerical response to the question, "After you left the recovery room, were you sick? If so, how many hours did you feel sick?"

Postoperative Nausea and Vomiting (PONV)

Conceptual definition: the experience of nausea and/or vomiting after surgery

Operational definition: any verbal report of feeling sick to one's stomach and/or expelling gastric contents within 24 hours after emergence from a general anesthetic

Vomiting

Conceptual definition: the expulsion or the attempt at expulsion of gastric contents via the mouth, resulting from the stimulation of the vomiting reflex (Berne & Levy, 1993)

Operational definition: in the PACU, the visible result of expelling gastric contents or the attempt to throw up (retching) will be recorded by the PACU nurse; after

discharge from the PACU, the verbal numerical response to the question, "How many times did you throw up after leaving the recovery room?" (For this study, one episode of vomiting will end when there is a rest period free of retching or vomiting for 5 minutes.)

Hypotheses

Hypothesis: There is a difference in the incidence of PONV when ondansetron is administered prior to induction versus administration at emergence from general anesthesia.

Null Hypothesis: There is no difference in the incidence of PONV when ondansetron is administered prior to induction versus administration at emergence from general anesthesia.

Significance of the Problem

PONV and its concomitant complications pose valid medical risks. One major concern is aspiration pneumonitis. This is a common complication of PONV that results from the aspiration of gastric contents, particularly when airway reflexes are marginal. It results in increased morbidity and sometimes mortality (Miller, 1994). PONV also places patients undergoing certain surgical procedures at increased risk. The act of vomiting can elevate central venous pressure leading to an increase in intracranial pressure and intraocular pressure that may damage delicate surgical

repairs, ultimately increasing morbidity (Miller, 1994). PONV can stimulate the sympathetic nervous system, increasing both the heart rate and the blood pressure, which stresses the myocardium. Conversely, gagging and retching can activate the parasympathetic nervous system resulting in bradycardia and hypotension. Another medical concern is increased intra-abdominal pressure causing patient discomfort and possibly resulting in wound dehiscence. All of these medical complications of PONV are legitimate concerns for health care providers and patients alike (Barash, Cullen, & Stoelting, 1992).

According to Orkin (1992), patients rate PONV as their primary concern postoperatively. Patient awareness regarding the availability of antiemetic agents makes them unwilling to suffer the discomfort of nausea and vomiting. Patients often vividly recall the PONV that they had experienced with prior surgeries. This experience can alter their attitude toward an otherwise successful surgery (Kenny, 1994). All of these factors (discomfort, patient and hospital costs, medical risks) make the prevention of PONV a meaningful endeavor in the treatment and well-being of patients.

Ondansetron has been shown to be successful in the treatment of PONV. However, the most effective timing of

administration is yet to be determined (Joslyn, 1994). The variability in the peak effect lends to the difficulty in determining the most appropriate time to administer ondansetron.

Assumptions

In this study, the following assumptions were made:

1. The act of vomiting was a result of nervous stimulation due to the activation of mechanical and chemical receptors.
2. All emetic agents have an equal ability for causing nausea and vomiting.
3. The vomiting center was equally sensitive to all neural stimulation.
4. Once the vomiting center was stimulated, an emetic episode would result.
5. Antiemetics exert their primary effect at the CTZ.
6. Randomization of the two groups eliminated bias and aided in the attainment of similar representative samples
7. Patients responded similarly to the anesthetic technique.

Limitations

1. A limitation of this study was the type of sample. It was a convenience sample drawn from U. S. Army medical

treatment facilities and it may not be representative of the general surgical population. Therefore, the results of this study may not be generalizable beyond the sample's characteristics.

2. The type of surgery was not controlled and may have influenced PONV.

Summary

PONV is a common and sometimes costly side effect of general anesthesia (Kenny, 1994). Many of the medications used during general anesthesia act on chemoreceptors within the body to cause vomiting. Ondansetron is theorized to act as an antagonist at the 5HT3 chemoreceptors located on both the CTZ and the vagal afferents of the gastrointestinal tract. This study compared different administration times of ondansetron and the incidence of PONV associated with those times of administration. With the relatively new use of ondansetron in the prevention and treatment of PONV, the most effective time of administration has yet to be determined.

CHAPTER II

Review of Related Literature

Historically, the majority of studies have addressed ondansetron administration in the setting of chemotherapy-induced nausea and vomiting (CINV). Cancer patients experience CINV on a frequent and severe basis, therefore, this population lends itself to the study of antiemetic agents. Treatment of CINV with conventional antiemetic agents leads to an overall success rate of 60% (Dicato & Freeman, 1992). The use of ondansetron for the treatment of CINV has been shown to have an overall success rate of up to 75% (Marty, Pouillart, & Scholl, 1990). As a result of the effectiveness of ondansetron in the treatment of CINV, its use has expanded to the treatment of PONV. The introduction of ondansetron in the perioperative setting is relatively new and the majority of studies have been conducted within the last five years. This literature review encompasses studies that compare the effectiveness of ondansetron to other antiemetics, determine the most effective dose of ondansetron for treatment of PONV, and evaluate the timing of ondansetron administration.

Ondansetron vs. Other Antiemetics

There are many drugs used in the treatment of PONV, the most common being metoclopramide and droperidol. Litman

et al. (1995) studied 57 American Society of Anesthesiologists (ASA classification is I - VI rating of patients, I = healthy and VI = organ donor) I and II children undergoing outpatient strabismus repair. Patients were randomly assigned to receive either ondansetron or droperidol shortly after induction of anesthesia. The number of episodes of emesis were documented. Ninety-four percent ($n=29$) of the patients who received ondansetron were emesis-free in the recovery room compared to 81% ($n = 21$) of the patients who received droperidol. A weakness of this study was the small sample size. No statistically significant difference was noted between the effectiveness of the two medications. Ondansetron was determined to be as effective as droperidol in reducing the frequency of emesis in children after strabismus repair.

Alon and Himmelseher (1992) studied 66 ASA I females in a randomized, double-blind comparison with metoclopramide 10 mg, droperidol 1.25 mg, and ondansetron 8 mg. Each drug was administered 10 minutes prior to induction in its recommended dose. Postoperatively, the incidence of vomiting was 54% ($n=12$) with metoclopramide, 45% ($n=10$) with droperidol, and 13% ($n=3$) with ondansetron ($p < 0.05$). A weakness of this study was the small sample size of 66 (22 patients in each group). Ondansetron was found to be the

most effective in decreasing the incidence of postoperative vomiting.

According to Naylor and Rudd (1992), both metoclopramide and droperidol have extrapyramidal side effects associated with them such as abnormal involuntary movements, alterations in muscle tone, and postural disturbances. Ondansetron has not been associated with these side effects. Like ondansetron, metoclopramide may also act at the 5HT₃ receptor at higher doses, but it primarily acts as a dopamine 2 receptor antagonist. When dopamine is antagonized, extrapyramidal effects may occur (Naylor & Rudd, 1992). Droperidol is associated with the same major side effects as metoclopramide, as well as with sedation and anxiety (Alon & Himmelseher, 1992). Based on the decreased incidence of PONV with ondansetron and the side effects associated with metoclopramide and droperidol, the authors concluded that ondansetron was more effective in preventing emetic sequelae (Alon & Himmelseher, 1992; Naylor & Rudd, 1992).

Dosage

A number of studies have attempted to determine the optimal dosage of ondansetron for the prophylactic treatment of PONV. Kovac et al. (1992) conducted a double-blind, placebo-controlled, dose-comparison study with 580 ASA I and

II female outpatients undergoing gynecological surgery with general anesthesia. The most effective dose for female outpatients with a negative history of PONV was found to be 4 mg IV. This dose was found to be 48% ($n = 70$) effective in controlling nausea and 86 % ($n = 125$) effective in controlling vomiting. The 8 mg dose was determined to be more effective for patients with a positive history of PONV. This dose was found to be 46% effective ($n=67$) in controlling nausea and 72% ($n=104$) effective in controlling vomiting.

McKenzie et al. (1993) conducted a study on 207 female ASA I, II, and III patients undergoing inpatient surgical procedures. The results showed ondansetron 4 mg IV to be the most effective in preventing postoperative vomiting compared to the placebo. Sixty percent ($n=49$) of the patients in the ondansetron group experienced no emetic episodes compared to 26% ($n=21$) of the patients in the placebo group ($p < 0.001$). According to the above studies, the optimal dose for the prevention of postoperative vomiting appears to be 4 mg IV.

The manufacturer (Glaxo Wellcome, 1995) also recommended 4 mg IV for the prevention of PONV, based on clinical trials conducted in the United States. A double-blind study involving 270 women undergoing laparoscopic

procedures was conducted using ondansetron IV compared to a saline placebo. Ondansetron 4 mg IV was given to 134 patients and a placebo was given to 136 patients. Forty-two percent ($n=56$) of the patients in the ondansetron group experienced no nausea compared to 29% ($n=39$) of the patients in the placebo group ($p=0.002$). Seventy-six percent ($n=103$) of the patients in the ondansetron group experienced no emetic episodes compared to 46% ($n=64$) in the placebo group (Glaxo Wellcome, 1995).

Ondansetron Administration at Induction

Ondansetron has been administered prior to the induction of anesthesia for the prevention of PONV. The literature regarding the timing of administration has focused mainly on induction. The rationale behind the timing was that a more accurate assessment of the patient could be obtained if they were conscious and their autonomic nervous systems were intact (Joslyn, 1994).

Kovac et al. (1992) conducted a double-blind, placebo-controlled study on 580 ASA I and II female patients undergoing gynecological surgery. Patients received either ondansetron 1 mg, 4 mg, 8 mg, or placebo (saline) IV immediately before induction. A barbiturate was used for induction. All patients received a narcotic and a neuromuscular blocking agent. Anesthesia was maintained

with oxygen and nitrous oxide. The use of isoflurane was optional. All patients received a standard reversal agent. Episodes of nausea were measured preoperatively and postoperatively with a linear scale: 0 = no nausea and 10 = worst nausea. Strengths of this study included the large sample size ($n=580$) and the control for age, surgery, weight, operative site, and type of surgery. These variables have been associated with a significant increase in the incidence of PONV. A limitation of this study was the lack of explanation regarding the method of controlling for these variables. Another limitation of this study was the optional use of isoflurane because inhalational anesthetics are well-known emetics (Kenny, 1994). This study found that ondansetron 4 mg IV was 80% ($n=116$) effective in preventing PONV compared to 8 mg IV at 75% ($n=94$) when given at induction ($p < 0.05$).

Another study looked at ondansetron 4 mg IV versus a saline placebo (Suen et al., 1993). Two hundred and ten ASA I and II Asian female patients undergoing gynecological laparoscopy for sterilization or diagnostic purposes were studied. Patients were excluded if they received opioids 24 hours preoperatively. No premedications were given the night prior to surgery. All patients received fentanyl, atracurium, and thiopental for induction. All patients were

intubated and anesthesia was maintained with isoflurane and nitrous oxide. All patients were reversed with neostigmine and atropine. Nausea was measured using a verbal numeric scale (0 = no nausea, 10 = worst nausea ever experienced). A strength of the study was that it controlled for all medications given preoperatively and intraoperatively. Controlling for medications limited the confounding variables that may have influenced the incidence of PONV. A weakness of this study was that the women undergoing the sterilization procedure received more opioids than the women undergoing laparoscopy for diagnostic procedures. Opioids are well-known emetic agents, significantly increasing the incidence of PONV (Kenny, 1994). Suen et al. (1994) found that ondansetron 4 mg IV was more effective than the placebo in preventing nausea ($p < 0.05$) and vomiting ($p < .01$) throughout the 24 hour period after surgery.

Pearman (1994) conducted two double-blind, placebo-controlled studies. The first study involved 580 ASA I and II female patients who underwent the same minor gynecological laparoscopic surgery (Pearman, 1994). The second study involved 468 ASA I and II male patients over 12 years of age who underwent various outpatient surgeries (Pearman, 1994). Patients were excluded if they had received antiemetics 24 hours prior to surgery. In both

studies, patients received ondansetron 1 mg, 4 mg, 8 mg, or a placebo IV immediately before induction. Nausea was measured using a scale from 0 (no nausea) to 10 (worst nausea) (Pearman, 1994). Vomiting was measured by the number of episodes. Ondansetron 4 mg IV was found to be the optimal prophylactic dose and was found to be more effective than the placebo ($p \leq 0.05$). Strengths of this study included that all patients had standardized induction medications and were intubated. A weakness of this study involved the optional use of the inhalational agent isoflurane during maintenance. This may have confounded the results because inhalational agents are well-known emetics. Another weakness of this study was the lack of reliability and validity of the nausea scale.

Khalil et al. (1994) conducted a double-blind, placebo-controlled study on 589 ASA I and II female patients undergoing gynecological surgery. The patients were stratified into three groups based on their history of PONV (no anesthetic experience, $n = 121$; history of PONV, $n = 304$, no history of PONV, $n = 164$). Patients received no premedications. Before patients entered the operating room, they were evaluated for nausea severity using an 11-point whole number scale: 0 = no nausea, 10 = the worst possible nausea. Vomiting was measured by the number of emetic

episodes. Patients were randomized to receive ondansetron 1 mg, 4 mg, 8 mg, or placebo IV immediately before induction. The induction protocol was the same for all patients, which included an IV barbiturate, a neuromuscular blocker, an opioid, and isoflurane. All patients were intubated at the beginning of the procedure. All patients received the same intraoperative medications. At the end of the procedure, residual neuromuscular blockade was reversed with any clinically available anticholinesterase. Seventy-six percent ($n=135$) of the patients in the ondansetron 1 mg group experienced no emetic episodes compared to 77% ($n = 140$) for the ondansetron 4 mg group and 75% ($n = 131$) for the ondansetron 8 mg group ($p < 0.05$). Only 60% ($n = 113$) of the patients in the placebo group experienced no emesis. Ondansetron 4 mg IV was found to be the optimal prophylactic dose ($p < 0.05$) in all groups studied.

The strength of this study was the separate evaluation of women with a history of PONV. This is valuable information because this population of patients is already predisposed to an increased incidence of PONV. Another strength of this study was the comprehensive preoperative and induction protocol, which eliminated some of the possible variables, some of which may have predisposed patients to PONV. A weakness of this study was the lack of

control for the anticholinesterase used for reversal of neuromuscular blockade. This is significant because certain anticholinesterases, such as neostigmine, are associated with a higher incidence of PONV (Kenny, 1994).

Sung, Wetchler, Duncalf, and Joslyn (1993) studied 180 ASA I and II females scheduled for gynecological surgery. This was a double-blind, placebo-controlled pilot study examining the effectiveness of ondansetron IV in the prevention of PONV. Patients received ondansetron 8 mg or a placebo IV immediately before induction. Patients were monitored in the postanesthesia care unit (PACU) by a research observer and at home by telephone. Data collection encompassed the 24 hour period following emergence from anesthesia. All preoperative medications were controlled for in an attempt to exclude any emetic agents. All patients received standard induction agents to include thiopental, fentanyl, and succinylcholine. Anesthesia was maintained with nitrous oxide and opioids. The use of isoflurane was optional. Nausea was measured using a scale from 0 (no nausea) to 10 (worst nausea) and vomiting was measured by actual number of episodes. Sixty-two percent ($n=55$) of the patients in the ondansetron group experienced no emesis over the 24 hour study period compared to 40% ($n=36$) of the patients in the placebo group. Ondansetron 8

mg IV, prior to induction, was found to be more effective than the placebo in preventing PONV. A weakness of the study was the optional use of isoflurane because inhalational agents are well known emetics.

Women are two to four times more likely to experience PONV. In terms of specific surgical procedures, gynecological surgery carries the second highest incidence of PONV (58%), second only to abdominal surgery (70%). This combination of risk factors, women and gynecological procedures, further predisposes the patient to PONV (Kenny, 1994). The above studies evaluated the administration of ondansetron only at induction and did not evaluate its effectiveness at other possible administration times.

Ondansetron at Induction vs. Emergence

Sun, Wang, Klein, and White (1996) studied the timing of administration of ondansetron at induction versus at emergence. Sun et al. (1996) compared the relative effectiveness of ondansetron 4 mg IV at induction (when patients are initially anesthetized) versus at emergence (when patients are brought out of the anesthetized state). Sixty-eight outpatients undergoing elective ENT procedures were randomly assigned to one of three treatment groups. Group 1 received a saline placebo at both induction and emergence. Group 2 received ondansetron at induction and

saline placebo at emergence. Group 3 received saline placebo at induction and ondansetron at emergence. The incidence of emesis for Group 1 was 14% in the recovery room and 12% over the 24 hour period following surgery. The incidence of emesis for Group 2 was 24% in the recovery room and 6% over the 24 hour period following surgery. The incidence of emesis for Group 3 was 8% in the recovery room and 5% in the 24 hour period following surgery. They found no significant difference between the induction and emergence groups, however, they found that ondansetron given at emergence was significantly different from the control group (which did not receive ondansetron) in decreasing the need for rescue antiemetics in the PACU.

This data was analyzed using ANOVA and Chi-square testing with p values < 0.05 considered significant. Interestingly, data from the recovery room showed the placebo (emesis = 14%) to be more effective in preventing emesis than ondansetron (emesis = 24%) given at induction. They made recommendations for the use of ondansetron at emergence rather than at induction because of the significant difference ($p < 0.05$) between the control group and the emergence group. A weakness of this study was the small sample size.

Postoperative Administration

Scuderi et al. (1993) studied 500 ASA I and II patients who experienced PONV within 2 hours of admission to the PACU. Patients were stratified by gender and received ondansetron 1 mg, 4 mg, 8 mg, or placebo IV in a randomized, double-blind manner in response to PONV. Some patients (number not reported) received a premedication of midazolam, fentanyl, or alfentanil. A standard general endotracheal anesthesia induction consisted of an induction agent (thiopental, thiamylal, or methohexital), an opioid (morphine, fentanyl, or alfentanil), and nitrous oxide. Isoflurane and neuromuscular blocking agents were administered as necessary. Reversal of a neuromuscular blockade was achieved with neostigmine or edrophonium with glycopyrrolate or atropine. Nausea was rated postoperatively with a whole number linear scale: 0 (no nausea) to 10 (worst nausea) and vomiting was assessed and recorded as the number of episodes. Forty-two percent ($n=52$) of patients in the ondansetron 1 mg group experienced no further emetic episodes. Forty-eight percent of the patients in both the ondansetron 4 mg group ($n=60$) and the ondansetron 8 mg group ($n=60$) experienced no further emetic episodes. Only 15% of the placebo group ($n=19$) experienced no further emetic episodes. All doses tested were significantly more effective than the placebo in

treating PONV ($p < 0.001$). Strengths of this study were the large sample size and the use of a standard induction technique. Weaknesses of this study included the use of an inhalation anesthetic (isoflurane) and neostigmine for neuromuscular blockade reversal, both of which are associated with a high rate of PONV (Kenny, 1994).

Summary

The literature review has addressed studies comparing the effectiveness of ondansetron to other antiemetics, the optimal dosage of ondansetron, and the most effective time of administration. Studies have shown that ondansetron is as effective as metoclopramide and droperidol for the treatment of PONV with fewer side effects (Alon & Himmelseher, 1992; Litman et al., 1995; Naylor & Rudd, 1992). Ondansetron 4 mg IV was found to be more effective for PONV, regardless of the time of administration (Kovac et al., 1992; McKenzie, 1993; Glaxo Wellcome, 1995). Ondansetron 4 mg IV was found to be more effective than the placebo when given at induction (Khalil et al., 1994; Kovac et al., 1992; Pearman, 1994; Suen et al., 1994). Only one study (Sun et al., 1996) addressed the benefit of administering ondansetron at induction versus emergence. Results showed that ondansetron was more effective when given at emergence versus at induction in the prevention of

PONV. When comparing various doses of ondansetron to a saline placebo, ondansetron was found to more effective regardless of the dose, in the treatment of PONV (Scuderi et al., 1993). There is a lack of research related to the effectiveness of ondansetron given at induction versus at emergence from general endotracheal anesthesia. The results of this research study will provide information to the body of knowledge regarding the optimal timing of ondansetron administration.

Methodology

This was a prospective, randomized, double-blind study. The purpose of this study was to determine if ondansetron was more effective in decreasing PONV when administered prior to induction of general anesthesia versus at emergence. This chapter describes the population, sample, setting, and methods used in this study. It also covers the instrumentation, procedure for data collection, protection of human subjects, design, and proposed data analysis.

Population, Sample, and Setting

The population included military health care beneficiaries presenting for elective inpatient and outpatient surgery at selected military hospitals. The sample was a convenience sample drawn from the population who met the criteria for the study and agreed to participate. The settings included Walter Reed Army Medical Center (WRAMC), Kimbrough Ambulatory Care Center (KACC), and DeWitt Army Community Hospital (DACH).

During the preanesthetic interview, on the day of surgery, patients were asked to participate in the study. Once the patient agreed to participate, they were assigned a study number in the order that they presented for surgery. Each study number was randomly assigned to one of two groups. The researchers were blinded to group assignment

and patient assignment was randomized to prevent selection bias. Group 1 received ondansetron 4 mg on induction and saline (2 cc) at emergence. Group 2 received saline (2 cc) at induction and ondansetron 4 mg at emergence. The assistant director (AD) of the Graduate Program in Anesthesia Nursing at WRAMC (or a designated alternate) maintained the record of group assignment. A comparison of the two group means was completed upon conclusion of data collection to determine the difference of the incidence of PONV.

Each study group contained 75 patients for a total sample size of 150. The sample size estimate was calculated based on a study by Sun et al. (1996). This study was most closely related to this proposal. Sun et al. (1996) recorded the incidence of PONV and assessed the effectiveness of ondansetron based on the timing of administration either at induction or emergence. Sun et al. (1996) determined a 20% difference to be significant. The sample size estimate for this study was based on the Sun et al. (1996) determination of significance. The power analysis for this study was prepared using the Number Cruncher Statistical System - Power Analysis & Sample Size (NCSS-PASS), Version 1.0.

Inclusion Criteria

Inclusion criteria were established to control for possible extraneous variables. ASA classifications were chosen in order to select patients without severe disease that may confound the findings. Both males and females were included to prevent a gender bias. The age range of 18 years and older was chosen due to the added complexity of studying a pediatric population. General anesthesia was selected because there is a higher incidence of PONV than with regional and local anesthesia. Emergency procedures were excluded because of the difficulty in obtaining informed consent. Data from emergency patients may be influenced by the emergency conditions. Patients not fluent in the English language require the use of interpreters for data collection and informed consent. The inclusion criteria are listed below:

1. ASA I, II, or III
2. Male or female, eligible for military health care
3. 18 years or older
4. Non-emergency surgical procedures
5. General endotracheal anesthesia
6. Scheduled for either inpatient or outpatient surgery
7. Able to speak and read the English language
8. Consented to participation in the study

Exclusion Criteria

Exclusion criteria were selected to control for factors that may skew results of the study. A documented allergy to the drugs used in this study were excluded. Patients with a history of malignant hyperthermia were excluded because of the absolute contraindication to a general anesthetic technique. According to literature from the manufacturer, no adequate and well-controlled studies for teratogenic effects have been conducted in pregnant patients therefore pregnant females were excluded. Patient refusal of the technique of general anesthesia or participation in the study excluded them from the study. Admission to the SICU may require prolonged intubation therefore data collection would be hindered. The exclusion criterion are listed below.

1. Patients with known allergies to ondansetron or any of the protocol medications
2. Patients with a known history of malignant hyperthermia
3. Pregnant females
4. Patient refusal
5. Planned SICU admission

Instrumentation

This study focused on the number of episodes of nausea and vomiting in the postoperative period with an end-point of 24 hours post-emergence. For this study, nausea was defined as "feeling sick to your stomach". For this study, vomiting was defined as the visible result of throwing up gastric contents or the attempt to throw up (retching). Data regarding episodes of reported nausea and vomiting were assessed using a script to assure standardization of data collection (see Appendix B). Data was documented on the data collection sheet (see Appendix C) throughout the recovery room stay by recovery room nurses who had been educated on the method of data collection.

Investigators communicated with patients by phone or in person using a script (see Appendix D) regarding the episodes of nausea and vomiting that occurred during the 24 hour post-emergence period. The data collection sheet included information regarding the following variables; age, gender, ASA category, weight, ethnicity, type and length of surgery, history of PONV, and type and amount of anesthesia. Cohen, Duncan, Deboer, & Tweed (1994) conducted a postoperative interview of over 16,000 patients and found an increased incidence of PONV associated with these variables. Careful documentation of these variables may provide valuable information for correlative retrospective analysis.

Procedure for Gathering Data

The procedure for data collection was as follows:

1. Patients were asked to participate in the study by one of the investigators involved with this study on the day of surgery (see Appendix E). Informed consent was obtained at that time.
2. A regimented procedure for anesthetic administration was used in order to reduce possible influences. The study drug was administered just prior to any induction agent (Group 1) and just prior to extubation (Group 2). All participating investigators used a regimented experimental procedure (see Appendix F) for induction, maintenance, emergence, and postoperative procedural sequences.
3. Episodes of PONV were recorded by the recovery room nurses (including phase II recovery room nurses at KACC and DACH) who were trained in the data collection process by the study investigators (see Appendix G). Recovery room nurses used a script with the data collection sheet. Data collection (including documentation) took approximately 1 minute per interaction.
4. The investigators retrieved the data collection sheets from the recovery room at the end of each operative day and checked for completeness and clarity of documentation.
5. Each patient was contacted (either in person or by

telephone if discharged) at the 24 hour post-emergence data collection end-point and asked to provide the number of episodes of nausea and vomiting.

6. Data collection occurred between January 1997 and May 1997.

Protection of Human Subjects

The study proposal was reviewed and approved by the Institutional Review Board of Walter Reed Army Medical Center. This study was reviewed by the University of Texas Houston - Health Science Center before beginning data collection. No data collection occurred prior to the approval of both institutions.

Consent was obtained in the preoperative holding area on the day of surgery. The potential risks and complications associated with general endotracheal anesthesia was explained again to the patient. To ensure privacy, patient names and social security numbers were kept confidential and were not used in the study. No patient was identified individually. Data was collected and analyzed, the information was documented in the thesis and placed in the University of Texas Houston-Health Science Center Library.

Study Design

This was a prospective, randomized, double-blind study. Members of a control group would be placed in jeopardy of increased risk of PONV and its concomitant complications; thus, the control group was excluded from this study.

Data Analysis

The demographic data was analyzed using Chi-Square (ASA, race), Student's *t*-test (age, BMI), and Fischer's Exact test (gender, PONV history). The cofactors were evaluated using Chi-Square (procedure category, PACU opiates), Fischer's Exact test (gastric tube), and the Mann Whitney test (length and anesthetic amounts). The Mann Whitney test was used to evaluate for a difference between the two groups used to compare the mean incidence of PONV between the two groups. It was also used to determine whether the differences between the means are statistically significant. Any conclusions, inferences, and findings will be based on these results.

Time Line

December 1996	Approval by the Walter Reed Institutional Review Board
January 1997	Approval by the University of Texas Houston - Health Science Center
November 1996	Approval by the Department of Clinical

Investigations / Human Use Committee.

January 1997	Data collection started
May 1997	Data collection complete
August 1997	Professional presentation at the American Association of Nurse Anesthetists convention
October 1997	Completion of final copy
January 1998	Graduation

Budget

The equipment and medications needed for the study were routinely stocked and in use. Any additional costs associated with this study were absorbed by WRAMC.

	FY 97	Total
Personnel		\$ 0.0
Equipment -		\$ 0.0
Consumable Supplies-		\$ 0.0
Travel -	\$ 1,000.00	
Reprints-	\$ 500.00	
TOTAL		\$1,500.00

Summary

This was a randomized, double-blind, descriptive study. Data was analyzed in order to determine if there was a difference in the effectiveness of ondansetron given at induction versus at emergence from general endotracheal anesthesia. Informed consent was obtained preoperatively. Investigators used a standardized technique for induction, maintenance, and emergence from general anesthesia. Assessment of the incidence of nausea and vomiting was initiated at emergence from general endotracheal anesthesia and continued for 24 hours thereafter. The data was analyzed using the Chi Square, Mann Whitney, Student's t test, and Fisher's Exact test.

CHAPTER IV

Analysis Of Data

The sample consisted of 150 military health care beneficiaries who presented for elective inpatient and outpatient surgery at selected military hospitals over a 5 month period. The data for 2 of the 150 patients was not utilized. Two patients were dropped from the study because their PACU and 24 hour post emergence data was insufficient. Five patients of the remaining 148 patients were unavailable at the 24 hour period for data collection but their PACU data was analyzed. The data for a total of 143 patients was complete with respect to PACU and 24 hour data with 71 patients in the induction group and 72 patients in the emergence group. This chapter will discuss and compare each group with regards to demographic characteristics, cofactors, and findings related to PACU and 24 hour post emergence data. All results in this chapter unless otherwise stated are mean values plus or minus standard deviation.

The following demographic characteristics are associated with an increased incidence of PONV: age under 50, BMI (Body Mass Index) over 28 kg/m², female gender, previous history of PONV, and ASA class 1 and 2 (Cohen et al., 1994). This study attempted to control for those

demographic characteristics associated with an increased incidence PONV (see Table 1 and 2). The demographic data were analyzed using Chi-Square (ASA, race), Student's *t*-test (age, BMI), and Fischer's Exact test (gender, PONV history).

The age range within the sample was 18 to 79 years of age with a mean age of 39. Within the induction group the age ranged from 18 to 79 and the emergence group ranged from 18 to 77 both having a mean age of 39. There was no significant difference ($p=0.56$) between the groups with regards to age.

The body mass index incorporates the patient's height and weight into a numerical value for which 28 kilograms per meter squared or above is considered obese (Stoeling & Dierdorf, 1993). The body mass index ranged from 18 to 37.5 kilograms per meter squared. Within the induction group the BMI ranged from 18 to 37.5 and 19 to 36 for the emergence group. The mean BMI for both groups was 26 kilograms per meter squared. There was no significant difference between the groups with respect to BMI ($p=0.14$).

Table 1

Demographic Characteristics of the Induction and Emergence
Groups (Age and BMI)

Characteristic	INDUCTION	EMERGENCE
Age (years)	group total (<u>n</u> =74)	group total (<u>n</u> =74)
<u>M</u>	39.2	39.9
<u>SD</u>	13.6	14.1
Height (inches)		
<u>M</u>	65.9	66.2
<u>SD</u>	3.6	3.9
Weight (kilograms)		
<u>M</u>	73.5	73.5
<u>SD</u>	13.9	13.5
Body Mass Index		
<u>M</u>	26.6	26.1
<u>SD</u>	4.3	3.8

ASA class was analyzed with the Chi-square statistical test. Within the sample, 97% (n=144) of patients were ASA classification 1 or 2 and the other 3% (n=5) were ASA class 3. Within the induction group there were 31 ASA I, 40 ASA II, and 2 ASA III patients. The emergence group contained 38 ASA I, 34 ASA II, and 3 ASA III patients.

The majority of the patients within the sample were Caucasian 65% (n=96), female 67% (n=99), and 87% (n=129) had

no previous history of PONV (see table 2). Within the two groups there was no significant difference ($p=0.48$) with respect to previous history of PONV. Patients with a history of PONV were evaluated in each group to determine if an increased incidence of PONV existed for these patients. There was no significant difference ($p=0.095$) in the incidence of PONV for this group of patients either in the PACU or 24 hours post emergence when compared to patients without a history of PONV. In summary we found no significant differences between the two groups with respect to the demographic characteristics analyzed.

Table 2

Demographic Characteristics of the Induction and Emergence
Groups (Race, Sex, and History of PONV)

CHARACTERISTICS	n	<u>INDUCTION</u> n (percentage)	<u>EMERGENCE</u> n (percentage)
<u>Race</u>	148	74	74
Caucasian	96	48 (64.9%)	48 (64.9%)
African American	39	19 (25.3%)	20 (27%)
Asian	4	3 (4.0 %)	1 (1.4%)
Hispanic	8	4 (5.3%)	4 (5.4%)
other	1	0	1 (1.4%)
<u>Sex</u>			
Female	99	50 (67.5%)	49 (66.2%)
Male	49	24 (32%)	25 (33.8%)
<u>History of PONV</u>			
positive	19	7 (9.4%)	12 (16.0%)
negative	129	67 (89.3%)	62 (84%)

*numerical values expressed as percentages of patients retained in the study

Other independent cofactors evaluated by this study included procedure category, the length of surgery, presence of a gastric tube, amounts of intraoperative medications and

a comparison of the use of postoperative medications. The selected cofactors were evaluated using Chi-Square (procedure category, PACU opioids), Fischer's Exact test (gastric tube), and the Mann Whitney U test (length and anesthetic amounts).

The incidence of PONV is increased with certain surgical procedures such as ear, nose, and throat (ENT), gynecological, and abdominal (Cohen et al, 1994 Kenny, 1994; Lerman, 1992) procedures. Therefore, the procedures were evaluated for even distribution between the two groups. Surgical procedures were categorized by anatomical location for ease of data analysis. The procedure categories were evaluated with the Chi square statistical test and found to have even distribution between the groups. The ear, nose and throat (ENT) category included 14.7% ($n=11$) of the induction group and 20% ($n=15$) for the emergence group. The gynecologic category included 21.3% ($n=16$) of the induction group and 18.9% ($n=14$) for the emergence group. This category consisted of any surgery on the female reproductive system except breast surgery which was included in the plastic category. The abdominal category consisted of 18% ($n=14$) of the induction group and 17% ($n=13$) of the emergence group and included any surgery in which the peritoneum was entered except for gynecological procedures.

The other surgical procedures were also analyzed. The extremity surgical category consisted of 1.3% ($n=1$) of the induction group and 8% ($n=6$) of the emergence group. The plastic surgery category included procedures performed to correct structural or cosmetic defects on visible portions of the body and contained 27% ($n=20$) of the induction group and 18.9% ($n=14$) of the emergence group. The neurologic category included laminectomies, and discectomies of which 16% ($n=12$) were in the induction group and 16.2% ($n=12$) were in the emergence group (see Table 3). There was no significant difference ($p=0.16$) in the distribution of the surgical procedures between the two groups.

Surgical procedures greater than 2 hours in length may contribute to an increased incidence of PONV (Cohen et al, 1994). The length of the surgery for this study was recorded as the time of induction of general anesthesia to the extubation of the patient in the operating room. The Mann Whitney test was used to evaluate if there was a difference in the length of surgery between the two groups. The length of the surgical procedures in the induction group was 2.9 ± 1.9 hours with a similar length in the emergence group of 2.4 ± 1.5 hours. There was no significant difference ($p=0.36$) between the two groups with respect to length of surgery.

Gastric tube placement perioperatively in the prevention of PONV is controversial and its benefit is questionable (Lerman, 1992) therefore its use was evaluated in this study. The purpose of an oral or nasal gastric tube is to remove excess gastric volume (air/liquid) to prevent gastrointestinal distention. The induction group had an oral/nasal gastric tube utilized in 84% ($n=63$) of the patients and the emergence group had an oral/nasal gastric tube used in 81% ($n=60$) of the patients (see Table 3).

Table 3

Percentage Comparison of Independent Cofactors for the
Induction and Emergence Groups

Cofactor	INDUCTION n (Percentage)	EMERGENCE n (Percentage)	TOTALS n(Percentage)
<u>Procedure (Category)</u>	.74	74	148
abdominal	14 (18.9%)	13 (17.6%)	27 (18.2%)
extremity	1 (1.4%)	6 (8.1%)	7 (4.8%)
gynecologic	16 (21.6%)	14 (18.9%)	30 (20.3%)
ear, nose and throat	11 (14.9%)	15 (20.3%)	26 (17.5%)
plastic	20 (27%)	14 (18.9%)	34 (23%)
neurologic	12 (16.2%)	12 (16.2%)	24 (16.2%)
<u>Gastric Tube (oral/nasal)</u>	74	74	148
used	63 (84%)	60 (81.1%)	123 (82.5%)
not used	12 (16%)	14 (18.9%)	26 (17.5%)

*numerical values expressed as percentages and number in
each group retained in the study

A comparison of the amounts of intraoperative medications administered to the two groups were evaluated. Prior to induction of general anesthesia, all patients received midazolam. For induction of general anesthesia all

patients received fentanyl, and propofol in a dose range of 2- 2.5 mg/kg. During the maintenance phase of anesthesia all patients received fentanyl as required.

The Mann Whitney-U test was used to evaluate for a difference in the doses of protocol medications administered. The mean midazolam dose in the induction group was $2.2 \text{ mg} \pm 0.63 \text{ mg}$ and $2.16 \text{ mg} \pm 0.77 \text{ mg}$ for the emergence group and there was no significant difference ($p=0.21$) found between these doses (see Figure 2). The mean dose of fentanyl was $487 \text{ ug} \pm 330$ in the induction group and $413 \text{ ug} \pm 302$ in the emergence group and there was no significant difference ($p=0.25$) found between these mean doses. All patients received muscle relaxation for intubation with either succinylcholine or vecuronium followed by vecuronium for maintenance as needed. For the induction group 26% ($n=19$) of patients received succinylcholine with a mean dose of $114 \text{ mg} \pm 17 \text{ mg}$ and 21% ($n=16$) of the emergence group received succinylcholine with a mean dose of $110 \text{ mg} \pm 26 \text{ mg}$ which does not represent a significant difference ($p=0.22$). Eighty-eight percent ($n=65$) of patients in the induction group and 87% ($n=64$) of patients in the emergence group received vecuronium which does not represent a significant difference ($p=0.52$). For the reversal of neuromuscular blockade 76% ($n=56$) of

patients in the induction group received neostigmine with 82% (n=61) of the patients in the emergence group receiving neostigmine which does not represent a significant

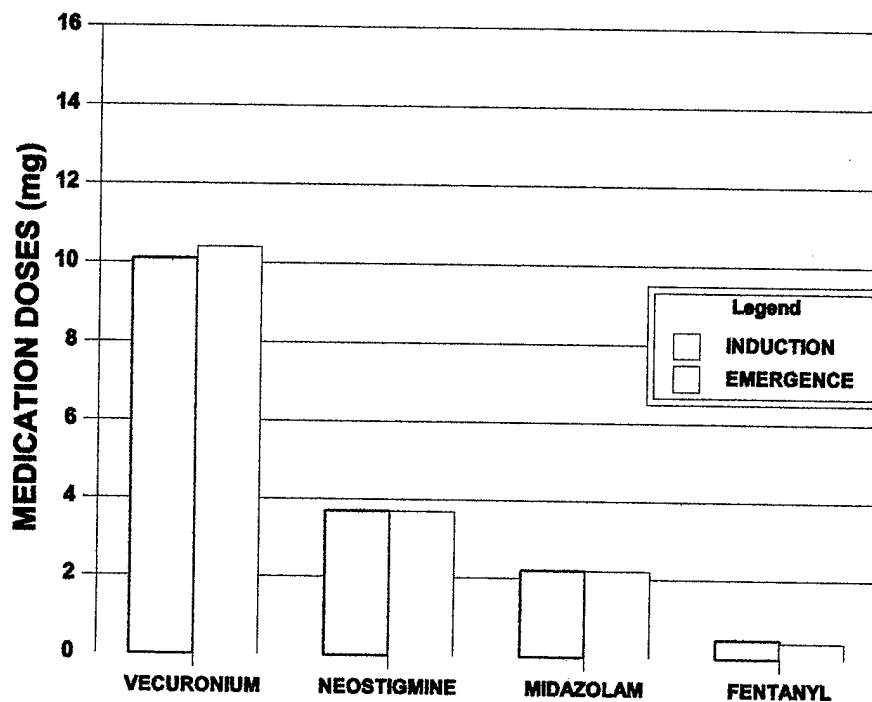


Figure 2. Comparison of the mean amounts of medication administered in the induction and emergence groups. The fentanyl dose was converted to milligrams to be included in the figure.*error bars are standard deviation

difference ($p=0.92$). There were no significant differences with respect to the amounts of intraoperative medications received by individuals within the two groups.

A comparison between postoperative pain medications administered to the two groups were evaluated as being used or not used. It is unclear if opioids prevent pain and therefore reduce the nausea associated with pain or if they are in themselves emetic agents which would cause PONV (Kenny, 1994; Joslyn, 1994). We assessed their use for postoperative pain control in the PACU to determine if there was an even distribution of their use between the two groups. The Chi square test was used to assess any difference in the use of opioids between the two groups. There were 23% ($n=17$) of the patients in the induction group who received morphine and 28% ($n=20$) of the patients in the emergence group received morphine with no significant difference between the groups ($p=0.57$). Ten percent ($n=7$) of patients in the induction group received meperidine and 3% ($n=3$) of the patients in the emergence group received meperidine which did not represent a significant difference ($p=0.16$). Fentanyl was administered to 4% ($n=3$) of the

patients in the induction group and 4% ($n=3$) of patients in the emergence group, again no significant was found ($p=0.99$).

The analysis of the demographic data provided an objective measure of the two groups. No significant difference between the two groups were found with respect to any of the demographic or analyzed cofactors. The groups contained even distribution of characteristics and cofactors. This lends strength to the study results, however it is impossible to account for all possible cofactors.

Findings

This study addressed the hypothesis, that there is a difference in the incidence of PONV when ondansetron is administered prior to induction versus administration at emergence from general anesthesia. Thus the null hypothesis is that there is no difference in the incidence of PONV when ondansetron is administered prior to induction versus administration at emergence from general anesthesia. Data was collected at the end of the PACU stay and 24 hours later. To test this set of hypotheses several different measurements of PONV were assessed for these two time periods.

Measurement of PONV in the PACU included the number of

vomiting episodes, presence of nausea, the use of rescue antiemetic medications for nausea and vomiting. The Mann Whitney-U test was used to evaluate for a difference between the two groups for any of these variables. The PACU data was analyzed for a total of 148 patients with 74 patients in the emergence group and 74 patients in the induction group.

For this study vomiting was defined as the expulsion or the attempt at expulsion of gastric contents via the mouth. Patients were asked the question "How many times did you vomit?" Three patients (4%) in the induction group vomited in the PACU as compared to six patients (8.2%) in the emergence group which does not represent a significant difference ($p=0.33$).

Nausea was measured by a simple "yes" or "no" response to the question "Do you feel sick to your stomach?". Nausea was reported for the PACU as being present or absent during the recovery room stay. There was a similar incidence of nausea in the PACU for both groups 24.0% ($n=18$) in the induction group and 24.3% ($n=18$) for the emergence group. No significant difference ($p=0.99$) in the incidence of nausea between the two groups was found.

This study also looked at the use of antiemetics to rescue patients from episodes of nausea and vomiting. Empirically the use of antiemetics should correlate with the

overall incidence of PONV in the PACU. Therefore, the assessment of antiemetic administration to patients in the study provides another important indicator of the presence of PONV during the PACU stay. The decision to administer a rescue antiemetic was delegated to the PACU nurses. The PACU nurses were blinded to group assignment to prevent the development of bias. In the PACU there was an equal incidence of antiemetic rescue for the induction and emergence groups 17.5% ($n=13$) in each group, and therefore no significance was found ($p=0.99$).

Measurement of PONV for the 24 hour post emergence period included an assessment of the number of times the patient felt nauseated, hours of nausea, the number of episodes of vomiting, and the use of antiemetics. The 24 hour post emergence data was analyzed for a total of 143 patients with 71 patients in the induction group and 72 patients in the emergence group. The 24 hour data was analyzed with the Mann Whitney statistical test. The researchers collected this data by visiting the patients on the ward or calling them at home by phone.

The episodes of nausea were assessed at the 24 hour data collection point by the question: "After you left the recovery room, how many times did you feel sick to your stomach?"; Figure 3 shows the percentage of patients in each

group that had 0, 1 to 4, and greater than 4 episodes of nausea for the 24 hour period following surgery. These groupings were chosen for ease of data presentation because

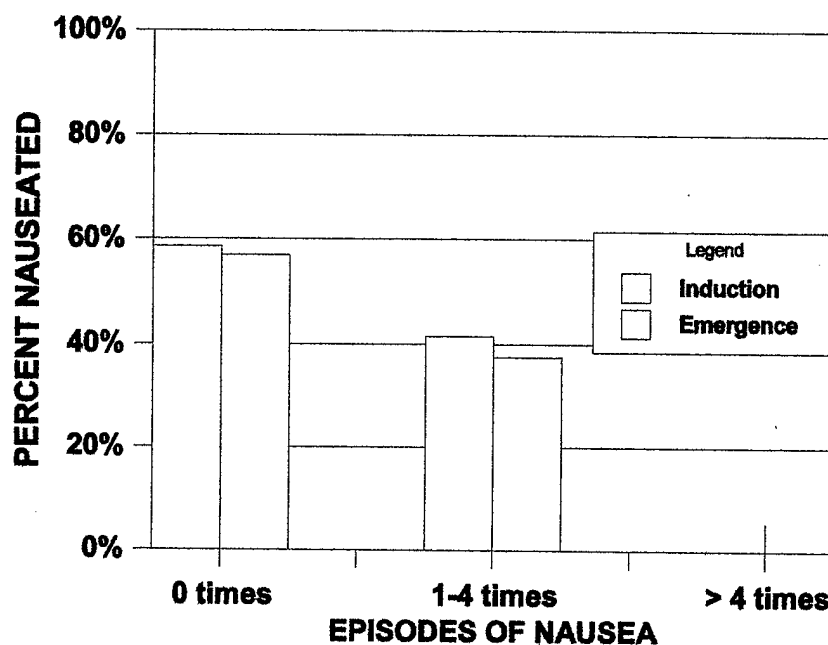


Figure 3. The incidence of nausea in the 24 hour post emergence period.

the induction group had no patients that had greater than 4 episodes of nausea. There was no significant difference ($p= 0.73$) with respect to nausea episodes between the induction and emergence group.

The total hours of nausea were assessed in the 24 hour post emergence period because of a potential to be nauseated continuously for several hours which would only be reported as a single episode of nausea. Patients were asked the question, "How many hours of nausea (feeling sick to your stomach) did you experience?" The mean number of hours of nausea for the 24 hour period was 1.12 ± 4.1 hours in the induction group and 1.54 ± 3.9 hours in the emergence group. There was no significant difference ($p=0.42$) in the hours of nausea between the induction and emergence groups.

An incidental finding during the 24 hour period revealed a shorter duration of nausea for patients that received ondansetron at induction and in the PACU as compared to patients who received ondansetron at emergence and in the PACU. These patients received a PACU 4 mg dose of ondansetron as a rescue antiemetic. There were 13 patients in the induction group who were rescued with

ondanseron in the PACU and of these patients only 31% ($n=4$) experienced more than 1 hour of nausea in the 24 hour post emergence period. The mean hours of nausea for the induction sub-group was 2.2 ± 3.9 hours. There were 12 patients in the emergence group who were rescued with ondansetron in the PACU and in this group 75% ($n=9$) of the patients experienced more than one hour of nausea in the 24 hour post emergence period. The mean hours of nausea for the emergence sub-group was 4.06 ± 3.9 hours. The Mann-Whitney test revealed a significant difference ($p=0.001$) between the two groups with respect to the hours of nausea in the 24 hour post emergence period. This difference is of clinical interest, however, these findings are preliminary and should be evaluated under a controlled scientific study. The incidence of vomiting was assessed by the question, "How many times did you throw up or vomit since you left the recovery room?" The incidence of vomiting for the 24 hours post emergence period for the induction group was 23% ($n=16$) and 15.3% ($n=11$) for the emergence group. The episodes of vomiting during the 24 period was expressed as a percentage and analyzed as being present or absent for the time period because a small number of patients in each group experienced vomiting. There was no significant difference ($p=0.26$) in the episodes of

vomiting between the induction and emergence groups.

The use of antiemetics during the 24 hour post emergence period was recorded because of the potential to effect the incidence of PONV. The patients were asked the question, "Did the nurses give you any medication or did you take any medicine to help with nausea and vomiting after you left the recovery room?" Ten percent ($n=7$) of patients in the induction group and 15% ($n=11$) patients in the emergence group took antiemetics for nausea and/or vomiting. There was no significant difference ($p=0.45$) in the use of antiemetics between the two groups.

Summary

In summary, this study found there to be no difference in nausea and vomiting between the induction group and the emergence group. Therefore, this study accepts the null hypothesis because there is no difference in the incidence of PONV when ondansetron is administered prior to induction versus administration at emergence from general anesthesia. The demographic data collected was age, race, gender, BMI, previous history of PONV, and ASA classification which are all known to have an effect on PONV (Cohen et al, 1994). There was even distribution with regard to these factors between the induction and emergence groups. Data was collected on the type and length of surgical procedures and

again the groups were similar. The patients in both groups had similar amounts of anesthetic agents. Patients were evaluated in the PACU and a similar incidence of nausea, vomiting, and use of antiemetics found. Additionally opioid use was similar between the groups. Patients were also evaluated 24 hours post emergence and a similar incidence of nausea, vomiting and use of antiemetics was found.

CHAPTER V

Discussion, Conclusions, Implications, and Recommendations

This study addressed the timing of ondansetron administration to determine if there was a difference in the incidence of PONV when ondansetron was administered at induction compared to administration of ondansetron at emergence from general anesthesia. This chapter will discuss the problem studied, the conceptual model in relation to the hypothesis, and will compare the findings of this study and those of related literature. This chapter also points out the strengths and weaknesses of this study as well as discusses the conclusions, implications, and recommendations for future research.

Discussion

Post operative nausea and vomiting is an important problem to those interested in controlling the increasing costs of hospitalization (Hirsch, 1994). PONV increases the costs of hospitalization by increasing the time spent in recovery along with a concomitant increase in staffing requirements, drugs, and supplies. It also results in

nonproductive time in the operating room because of unnecessary delays. Preventing PONV would not only shorten hospital stays, it would also conserve hospital resources and increase productivity in the operating room and recovery room (Sanchez & Hirsch, 1992). Ondansetron (Zofran) is an antiemetic which has commonly been used for cancer patients undergoing chemotherapy treatment. Its use in the prevention and treatment of PONV is relatively new and optimal administration times have yet to be determined (Dupeyron et al., 1993; Rust & Cohen, 1994).

This study was guided by a physiologic conceptual model of nausea and vomiting. This framework addressed the influences that contribute to nausea and vomiting. There are many nervous tissues within the body that are associated with causing nausea and vomiting when stimulated. The vomiting center, which is in the medulla, is the core of this framework and is influenced directly and indirectly by higher centers, the chemoreceptor trigger zone (CTZ), emetics, antiemetics, and a variety of mechanical and chemical receptors (Berne & Levy, 1993). The CTZ is located in the area postrema on the blood side of the blood brain barrier near the floor of the fourth ventricle. Because of this location, it is easily accessed by chemicals in the blood (Berne & Levy, 1993). Five-hydroxytryptamine subtype

3 (5HT₃) receptors are located on the CTZ and in other areas within the body (Naylor & Inall, 1994). The neurotransmitter serotonin (5HT) which acts on the CTZ seems to be involved in a common pathway which may be responsible for the mediation of PONV (Naylor & Inall, 1994).

The hypothesis of this study was: there is a difference in the incidence of PONV when ondansetron is administered prior to induction versus administration at emergence from general anesthesia. From the conceptual model it was assumed that ondansetron might be more effective if its action was initiated before the appearance of emetic agents. This assumption was based on the Clarke classical theory of receptors which states that for a drug to exert its effect it must occupy the receptor (Goodman & Gillman, 1996). Once an antagonist (ondansetron) occupies the receptor it takes more agonist (serotonin) to overcome the antagonist's effect and the reverse is also true (Goodman & Gillman, 1996). The results of this study demonstrate that ondansetron is effective in preventing PONV. It can be inferred that ondansetron is just as effective regardless of when the receptor is occupied since no difference in PONV was found when ondansetron was administered before or after the appearance of emetic agents.

The review of literature found up to a 50% incidence of PONV for patients undergoing general anesthesia (Quinn, Brown, Wallace, & Ashbury, 1994). In this study, the overall incidence of nausea for the induction group was 24.0% and 24.3% in the emergence group and the overall incidence of vomiting was 23% and 15 % respectively. The results of this study are supported by the findings of Sun, Wang, Klein and White (1996) which is the only published study that addresses the effectiveness of ondansetron related to its administration at induction or emergence. Sun et al. studied 68 outpatients undergoing elective ENT procedures. They compared the relative efficacy of a 4 mg dose of ondansetron IV at induction versus at emergence. They found no significant difference between the induction and emergence groups. However, they found that ondansetron given at emergence was significantly different from the control group in decreasing the need for rescue antiemetics in the PACU. They made recommendations for the use of ondansetron at emergence rather than at induction because of the significant difference ($p < 0.05$) between the control group and the emergence group.

Our study found the only significant difference between the induction and emergence group to be related to the duration of nausea in the 24 hour post emergence period. The hours of nausea were analyzed for those patients who received a

second dose of ondansetron for treatment of PONV in the PACU. This induction sub-group had fewer hours of nausea than the emergence group. This was the only instance when one timing option was better than the other. This may be clinically significant because 75% ($n=9$) of the emergence sub-group had greater than 1 hour of nausea as contrasted to 31% ($n=4$) of the induction sub-group.

An unpublished study by Byrant & Hosking (1997), studied 44 ASA I-III females undergoing laparoscopic surgery and found a significant difference ($p=0.007$) in the incidence of nausea in the PACU between a group of patients receiving ondansetron 30 minutes prior to surgery and a group that received ondansetron 30 minutes after the onset of surgery. They also looked at the incidence of PONV for a total of 4 hours post emergence and found no statistical significance.

One of the strengths of our study is the large sample size ($n=143$); the only other study to address the timing of ondansetron at induction and emergence had a smaller sample size ($n=75$). Another strength was the use of a double-blind randomized study design. Because the researchers and data collectors were blinded to which medication the patient received, the possibility of bias was eliminated during the data collection and group assignment portions of the study. This study also attempted to assess the similarity of

cofactors between each group regarding age, race, sex, height, BMI, ASA classification, amounts of medications, and history of PONV.

A weakness of this study was the lack of a control group for comparison of the overall incidence of PONV. The rationale for the absence of a control group was that members of a control group would be placed at increased risk for PONV and its concomitant complications since they would not receive an antiemetic. The use of a tool to evaluate the degree of PONV experienced by each group could have provided information on the effectiveness of ondansetron and a comparison of the degree of nausea experienced by the groups. This study was directed toward evaluating the presence or absence of PONV to determine the incidence for this selected sample. The involvement of many different types of surgeries and patient populations may have weakened the study by not focusing on a sample with a known high incidence of PONV. By focusing on these high risk groups the frequency of PONV may have been greater and therefore the findings may have revealed a clearer representation of the effectiveness of ondansetron. For this study patients with a history of PONV were compared to patients without a history of PONV and no significant difference ($p=0.095$) in the incidence of PONV was found. The study also involved

the use of several different PACU nurses ($n=20$), however, the data collection sheet contained the exact questions to be asked of patients at the end of their PACU stay. There is always the potential that PACU nurses may ask the questions in a different manner and therefore elicit a different response. No testing was completed to evaluate for interrater reliability among the 20 nurses. This study could have been further strengthened by using a small number of data collectors for whom interrater reliability was evaluated.

Conclusion

When ondansetron 4 mg IV is administered at induction or emergence from general endotracheal anesthesia, patients experience a similar incidence of PONV in the recovery room and up to 24 hours post emergence.

Implications for Nursing Practice

This study provides several implications for the profession of nursing. This study provides additional information to the body of knowledge related to the timing of ondansetron administration because few studies have focused on this area of research. This ongoing effort to prevent postoperative nausea and vomiting provides nurses the opportunity to take an active role in research that will lessen the discomforts and complications that this problem

presents to surgical patients.

In this age of cost containment the health care policies which are implemented are those which have been shown to be cost effective. Nurses must take an active role in providing answers to research questions which will effect the implementation of medical therapies. The cost of ondansetron may be outweighed by its effectiveness and its use may be warranted as a prophylaxis for those patients with a known history of PONV.

This research offers two options on administration times for ondansetron (Zofran). Anesthesia providers can have confidence that at these two administration times ondansetron's effectiveness in reducing the incidence of PONV is similar. This research provides personnel who provide perioperative care to surgical patients additional information to assist in the decision making process for the administration of ondansetron.

It also provides new questions for nurses involved in research. For example: those patients treated at induction and rescued in the PACU had fewer hours of postoperative nausea compared to patients treated at emergence and then rescued in the PACU. This finding raises an additional question of when is the optimal time of ondansetron administration.

Recommendations for Further Research

Many studies have been conducted concerning ondansetron's effectiveness and its use perioperatively. Few studies have been conducted comparing different administration times and its effect on PONV. This study should be repeated and should focus on patients and procedures associated with a high risk of PONV as well as utilize a standardized instrument for the evaluation of PONV. A future study should also explore the administration of ondansetron at induction and combined with a PACU dose as compared to administration at emergence combined with a PACU dose.

The majority of studies assessing PONV have been conducted on patients with a high risk of PONV. In the general surgical population the incidence of PONV is up to 50% (Quinn, et al., 1994). High risk groups can have up to a 70% to 80% incidence of PONV (Kenny, 1993). Repeating this study in a high risk population would promote a clearer differentiation between treatment groups.

The use of a standardized instrument is common practice in research conducted to evaluate PONV. An instrument allows researchers to capture a subjective experience and create an objective measure of PONV. This study focused on the incidence of PONV but failed to assess the degree of

PONV experienced by the patient. Therefore, future studies should incorporate an instrument to evaluate PONV.

The findings of this study stimulate additional questions about the timing of ondansetron administration. The shorter duration of nausea experienced by patients within the sub-groups represents an area of potential interest for the administration of ondansetron. The clinical significance of this finding has yet to be determined but it may represent a viable option for patients with a history of PONV. It follows that if patients have a history of PONV the administration of ondansetron at induction may be the more appropriate choice between the two administration options. This research provides the foundation for future studies and promotes the development of many research questions which will add to the body of knowledge in this area.

Mosby Year Book Inc.
1180 Westline Industrial Drive
St. Louis MISSOURI 63146

Permissions

25 April 96

APR 30 1996

To whom it may concern;

I am asking for permission to use a diagram in our research thesis. The diagram was in Physiology, by Berne and Levy, 1993 on page 640..figure 38-25. We are not using the exact diagram published but similar with our own ideas also in it. Thank you very much for your prompt attention.

Cathy Peuterbaugh

Cathy Peuterbaugh
11146 Vance Jackson #5107
San Antonio Tx 78230

Mosby-Year Book, Inc.
11830 Westline Industrial Drive
St. Louis, MO 63146

Permission is granted for non-exclusive use of the material specified, provided credit is given which acknowledges the author(s) or editor(s), title, edition, city, year of publication, and publisher.

5/10/96
Date

Patricia K. Ochamba
Permissions Department
Patricia K. Ochamba, Coordinator
Library Services and Permissions

APPENDIX A

Letter of Permission for Figure

APPENDIX B

Script for Data Collection by Recovery Room Nurses/Second

Stage Recovery Saff

"Do/Did you feel sick to your stomach ?"

"How many times did you vomit or throw up fluid from your stomach?"

APPENDIX C

Ondansetron Study Data Sheet

Date: Subject #: ASA:

Demographic DataSurgery/Anesthesia Data

Age: ____ Sex: ____

Procedure: ____ Length: ____ hrs

Nasogastric/ Orogastic Tube ____

Ht: ____ Wt: ____ BMI: ____

Agents: in addition to Forane and N20

Midazolam ____ mg, Flumazenil ____ mg

History of PONV(yes, no)

Fentanyl ____ mg Narcan ____ mg

Race: Caucasian, Black,

Muscle relaxant ____ Dose ____ mg

Hispanic, Asian, Other:

Reversal agent ____ Dose ____ mg

YES

NO

<p>Did the patient vomit in the recovery room ?</p> <p>Question: "How many times did you vomit or throw up fluid from your stomach?"</p>	<p>Clearly write the number of episodes in this space ()</p>	
---	---	--

Antiemetic choices #1. Ondansetron 4 mg (please consider using this drug first) #2. Metoclopramide 10 mg #3. Droperidol 0.625 mg	Circle the antiemetic that was administered: #1 #2 #3	
Did the patient receive an analgesic in the recovery room?	name of drug _____ dose _____ time _____	
Did the patient c/o nausea in recovery room? Question: “Do/Did you feel sick to your stomach ?”		

24 Hour Post-Emergence Data Collection End-Point

1. How many times did you feel nauseous? _____
2. How many times did you vomit? _____
3. What medication did you take for either nausea or vomiting? _____
4. How many hours (approximately) did you feel nauseous after leaving the RR to present? _____

APPENDIX D

Script for Obtaining 24 Hour Post-Emergence Data

Ask for patient by full name. "Hello, this is (your name and title). I am calling/visiting to follow up on the study you are in related to the nausea medication that we talked about yesterday. I have a few questions. Do you feel like talking now? Please be as accurate as you can. If you can't remember the information, that's ok, just let me know so we don't record wrong information."

"After you left the recovery room, how many times you throw up or vomit? Remember, one episode is every time you vomited or tried to throw up fluid from your stomach. If there was a rest period of five minutes with no vomiting or retching between when you started throwing up and you threw up again, that is counted as another episode. How many hours of nausea (feeling sick to your stomach) did you experience?; How many times did you feel sick to your

stomach? Remember, I don't want you to include the episodes in the recovery room. Did the nurses give you any medication or did you take any medicine to help with nausea and vomiting after you left the recovery room? "Thank you for participating in my study. We hope that the information you have given us is accurate so we can help other patients go through as little postoperative nausea and vomiting as possible."

APPENDIX E

Script for Obtaining Consent

"I am a student in the US Army Graduate Program in Anesthesia Nursing. My colleague and I are conducting a study to determine the best time to give Zofran (also called ondansetron). This medication is used to prevent or decrease the nausea and vomiting you may experience after surgery. We think there may be a difference in how effective the medicine is at preventing nausea and vomiting based on when it is given. If you choose to participate in this study you will receive Zofran, the only difference is the time that you will receive the medicine. You will receive the medicine either when you go to sleep or just before you awaken. Zofran, like all the other medicines we will use today is approved by the Food and Drug Administration. Zofran has very few side effects, stated simply it is safe. I want to assure you that you do not have to participate in this study and you will receive the same care and attention regardless of what decision you

make. Whether you choose to participate or not, any episode of nausea or vomiting will be treated. Would you be willing to participate?" (If the patient responds favorably, proceed with next paragraph.)

"Your participation will involve telling the nurses in the recovery room about any feelings of nausea which is feeling sick to your stomach or the need to vomit and telling them how many times you vomit. After you leave the recovery room you will need to record how many times you feel sick to your stomach or vomit during the next 24 hour period. My colleague or I will call or see you the next day and ask you about the number of times you felt sick to your stomach or threw up."

APPENDIX F

Induction Sequence

1. The AD was notified by the researcher that a new patient has given consent for the study and demographic data has been collected.
2. The AD was responsible for the preparation and labeling of the study medication and saline.
3. An IV line was started in the preoperative holding area. A preload of 0.9% NS or LR, 5-7 ml/kg, was administered (exact amount based on clinical situation).
4. As the IV was infusing, the anesthetist injected 4 mg of ondansetron or 2cc normal saline over 2-5 min. The anesthetist was blinded to what medication or solution they were giving to the patient. As a safeguard, the assistant director of the Graduate Program in Anesthesia Nursing at WRAMC or a designated alternate were unblinded to the contents of each syringe.
5. Patients were given midazolam 1-5 mg for anxiety as needed.
6. Patients were connected to monitoring equipment in the

operating room and baseline vital signs were recorded by the anesthetist as per anesthesia standard of practice.

7. Oxygen was adjusted to at least 6 L/min and a mask placed on the patient.

8. The patient was denitrogenated over 2 minutes or 4 vital capacity breaths as per anesthesia standard of practice.

9. If the anesthetist considered an opioid to be appropriate, fentanyl (1.0-5.0 ug/kg) were administered and recorded with patient data.

10. Induction agent is propofol (2.0-2.5 mg/kg)

11. The anesthetist then either ventilated or proceeded with neuromuscular blockade (if a rapid sequence intubation was indicated).

12. A neuromuscular blocker was then be administered to facilitate intubation.

13. The anesthetist had the option of using isoflurane, a potent inhalational agent, during induction.

14. An endotracheal tube was then placed and its position verified. The patient was then ventilated by assisted or controlled mode, based on the clinical decision of the anesthetist.

MAINTENANCE

1. Fentanyl was administered during the maintenance period at 2.0-15.0 ug/kg as needed.
2. If muscle relaxation was indicated, the anesthetist continued with a neuromuscular blocker.
3. Isoflurane, a potent inhalational agent, could have been used throughout the maintenance period with up to 70% nitrous oxide.
4. Patients were reversed from neuromuscular blockade, if clinically indicated, with neostigmine (0.04-0.08 mg/kg) and glycopyrrolate (0.01-0.02 mg/kg).

EMERGENCE

The patient received either ondansetron 4 mg IV or 2cc normal saline (over 2-5 minutes) just prior to extubation. The anesthetist will be blinded to the contents of the syringe.

POSTOPERATIVE

1. Patients received an opioid and/or a non-steroidal anti-inflammatory if indicated. Any analgesic given was recorded on the data sheet.
2. Data was recorded during the recovery room period and at the 24 hour post-emergence data collection end-point.

3. If the patient required a rescue drug for nausea or vomiting, the recovery room staff was encouraged to first use another dose of ondansetron 4 mg IV and/or metoclopramide 10 mg IV or 0.625 mg droperidol IV.

APPENDIX G

Script for Training Recovery Room/Second
Stage Recovery/Same Day Surgery Staff
In Data Collection Process

"We are conducting this study to determine if there is a difference in the effectiveness of ondansetron based on the time it is administered to patients. It is vital to our study to assess accurately how many episodes of nausea and/or vomiting patients experience in the recovery room. We are giving you a script to use when assessing for episodes of nausea and vomiting in the recovery room because we want to assure that all patients are treated exactly the same so as not to skew the information we collect for this study. Please adhere to the script each time you ask the patient about nausea or vomiting. Documentation of the presence or absence of nausea and the number of episodes of vomiting will be recorded on the Data Collection Sheet prior

to the discharge of the patient from the recovery room. Please do not add to, subtract from, or try to interpret the question for the patient, even if you feel like they are having trouble with the questions. Following this script may aid in decreasing subjectivity between data collectors. If we do not follow the script, information we gather may not be truly measurable or meaningful. I want to stress again that your role is essential and a very important part of this study and we appreciate your assistance and cooperation. Thank you."

"For this study we defined vomiting as the continuous effort by a patient to expel gastric contents through the mouth. Any 5 minute rest or pause period between episodes of vomiting, other than to take a breath, will constitute an additional episode of vomiting."

"For this study, we defined nausea as the feeling of a need to throw up/vomit or a complaint of feeling sick to the stomach by the patient."

"If you would like the results of this study, we will be happy to provide a presentation on an individual or group basis. You may contact us through the Walter Reed Army Medical Center Graduate Program in Anesthesia Nursing office at (202) 782-6481."

References

Alon, E. & Himmelseher, S. (1992). Ondansetron in the treatment of postoperative vomiting: A randomized, double-blind comparison with droperidol and metoclopramide.

Anesthesia and Analgesia, 75, 561- 565.

Barash, P., Cullen, B., & Stoelting, R. (1992).

Clinical Anesthesia (2nd ed.). Philadelphia: Lippincott.

Berne, R. M. & Levy, M. N. (1993). Physiology. St.

Louis: Mosby.

Bryant, P., & Hosking, M. (1997, August). Ondansetron:

Antiemetic efficacy and timing of administration. Poster session presented at the annual meeting of the American Association of Nurse Anesthetists, San Francisco, CA.

Cohen, M., Duncan, P., Deboer, D., & Tweed, A. (1994).

The postoperative interview: Assessing risk factors for nausea and vomiting. Anesthesia and Analgesia, 78, 7-18.

Dicato, M. A. & Freeman, A. J. (1992). Experience with ondansetron in chemotherapy and radiotherapy-induced emesis.

European Journal of Anaesthesiology, 9, (Supplement 6), 19-24.

Du Pen, S., Scuderi, P., Wetchler, B., Sung, Y. F.,

Mingus, M., Clayborn, L., Leslie, J., Talke, P., Apfelbaum, J., Sharifi-Azad, S., & Williams, M. (1992). Ondansetron in

the treatment of postoperative nausea and vomiting in ambulatory outpatients: A dose-comparative, stratified, multicentre study. European Journal of Anaesthesiology, 9, (Supplement 6), 55-62.

Dupeyron, J. P., Conseiller, C., Levarlet, M., Hemmingson, C., Schoeffler, P., Pedersonn, F. M., Gribomont, B., & Kaplan, L. A. (1993). The effect of oral ondansetron in the prevention of postoperative nausea and vomiting after major gynecological surgery performed under general anesthesia. Anesthesia, 48, 214-218.

Foster, S. D. & Jordan, L. M. (1994). Professional aspects of nurse anesthesia practice. Philadelphia: F. A. Davis.

Glaxo-Wellcome Inc. (Ed.). (1995). Ondansetron package insert. (Available from Cerenex Pharmaceuticals, Research Triangle Park, NC 27709)

Goodman Gillman, Alfred. (1996). Goodman & Gillman's, The pharmacological basis of therapeutics (9th ed). New York: McGraw Hill.

Guyton, A. C. & Hall, J. E. (1994). Textbook of medical physiology (9th ed.). Philadelphia: Saunders.

Hirsch, J. (1994). Impact of postoperative nausea and vomiting in the surgical setting. Anesthesia, 49, (Supplement), 30-33.

Joslyn, A. F. (1994). Ondansetron, clinical development for postoperative nausea and vomiting: Current studies and future directions. Anesthesia, 49, (Supplement), 34-37.

Kenny, G. N. C. (1994). Risk factors for postoperative nausea and vomiting. Anesthesia, 49, (Supplement), 6-10.

Khalil, S. N., Kataria, B., Pearson, K., Conahan, T., Kallar, S., Zahl, K., Gillies, B., Campbell, C., Brahen, N., Gilmour, I., & Templeton, D. (1994). Ondansetron prevents postoperative nausea and vomiting in women outpatients. Ambulatory Anesthesia, 79, 845-851.

Kovac, A., McKenzie, R., O'Connor, T., Duncalf, D., Angel, J., Gratz, I., Fagraeus, I., McLeskey, C., & Joslyn, A. F. (1992). Prophylactic intravenous ondansetron in female outpatients undergoing gynecological surgery: A multicentre dose-comparison study. European Journal of Anaesthesiology, 9, (Supplement 6), 37-47.

Lerman, J. (1992). Surgical and patient factors involved in postoperative nausea and vomiting. British Journal of Anaesthesia, 69, 24s-32s.

Lee, J.T. & Hirsch, J. D. (1992). Debilitation attribution to postoperative nausea and vomiting after discharge: Ambulatory surgery patients' perceptions. Poster presentation at the VII Annual Meeting of the Society of Ambulatory Anesthesia, Orlando, Florida.

Litman, R., Wu, C., Lee, A., Griswold, J., Voisine, R., & Marshall, C. (1995). Prevention of emesis after strabismus repair in children: A prospective, double blinded, randomized comparison of droperidol versus ondansetron. Journal of Clinical Anesthesia, 7, 58-62.

Marty, M., Pouillart, P. & Scholl, S. (1990). Comparison of the 5-hydroxytryptamine 3 antagonist ondansetron (GR38032F) with high dose metoclopramide in the control of cisplatin induced emesis. New England Journal of Medicine, 322, 816-821.

Melnick, B. (1988). Extrapyramidal reactions to low-dose droperidol. Anesthesiology, 69, 424-426.

McKenzie, R., Sharifi-Azad, S., Dershwitz, M., Miguel, R., Joslyn, A., Tantisira, B., Rosenblum, F., Rosow, C., Downs, J., Bowie, J., Sheahan, K., Odell, S., Lessin, J., DiBiase, P., & Nations, M. (1993). A randomized, double-blind pilot study examining the use of intravenous ondansetron in the prevention of postoperative nausea and vomiting in female patients. Journal of Clinical Anesthesia, 5, 30-36.

Miller, R. et al. (Ed.) (1994). Anesthesia (4th ed.) New York: Churchill Livingston.

Naylor, R. J. & Inall, F. C. (1994). The physiology of postoperative nausea and vomiting. Anesthesia, 49, 2-5.

Naylor, R.J. & Rudd, J.A. (1992). Pharmacology of ondansetron. European Journal of Anaesthesiology, 9, 3-10.

Orkin, F. K. (1992). What do patients want? Preferences for immediate postoperative recovery. Anesthesia and Analgesia, 74, S225.

Pearman, M. H. (1994). Single dose intravenous ondansetron in the prevention of postoperative nausea and vomiting. Anaesthesia, 49, 11-15.

Quinn, A.C., Brown, J.H., Wallace, P.G., Ashbury, A. J. (1994). Studies in postoperative sequelae. Nausea and vomiting-still a problem. Anaesthesia, 49, 62-65.

Rust, M., & Cohen, L. A. (1994). Single dose ondansetron in the prevention of postoperative nausea and emesis. Anaesthesia, 49, 16-23.

Sanchez, L.A. & Hirsch, J.D. (1992). Identification of cost consequences as the critical step in a cost of illness study: Postoperative nausea and vomiting in an ambulatory surgery center example. Journal of Research and Pharmaceutical Economics, 4, 41-53.

Scuderi, P., Wetchler, B., Sung, Y. F., Mingus, M., Du Pen, S., Claybon, L., Leslie, J., Talke, P., Apfelbaum, J., Sharifi-Azad, & S., Williams, M. (1993). Treatment of postoperative nausea and vomiting after outpatient surgery

with the 5-HT₃ antagonist ondansetron. Anesthesiology, 78, 15-20.

Shavari, M., Epstein, B. S., Weintraub, H. D., March, M.G., Peck, M., Kekoler, S., Conry, K. & Naully, J. S. (1992). Treatment of postoperative nausea and vomiting with IV ondansetron in outpatient surgery. Anesthesiology, 77, A46.

Stoelting, R., & Dierdorf, S. (1993). Anesthesia and co-existing disease (3rd ed.). New York: Churchill Livingston.

Suen, T. K. L., Gin, T. A., Chen, P. P., Rowbottoms, Y. M., Critchley, L. A. H., & Ray, A. K. (1994). Ondansetron 4 mg for the prevention of nausea and vomiting after minor laparoscopic gynecological surgery. Anesthesia and Intensive Care, 22, 142-146.

Sun, R., Wang, M., Klein, K. , & White, P. (1996). The effect of timing of ondansetron administration on efficacy in outpatients undergoing ENT surgery. Anesthesia and Analgesia, 82, S431

Sung, Y. F., Wetchler, B. V., Duncalf, D., & Joslyn, A. F. (1993). A double-blind, placebo-controlled pilot study examining the effectiveness of intravenous ondansetron in the prevention of postoperative nausea and emesis. Journal of Clinical Anesthesia, 5, 22-29.

VITAE

Catherine Elizabeth Peuterbaugh was born in Detroit, Michigan on August 5, 1962, the daughter of Robert Allen Douglas and Ann Mary Walker. She graduated from Oakwood High School in Dayton, Ohio in 1980. She received a Bachelor of Science in Nursing from Oakland University of Rochester, Michigan in 1986. In 1986, she married Kevin John Peuterbaugh of Utica, Michigan and they have a six year old child, Ian Andrew. She received an ROTC commission in 1984 and entered active duty in February, 1987. While stationed at Tripler Army Medical Center in Honolulu, Hawaii, she attended the Intensive Care Nursing Course. In 1989 she received a Masters in Health Service Administration from Central Michigan University. Her nursing experience includes intensive care nursing in both civilian and military hospitals. She is currently enrolled in the U.S. Army / University of Texas Houston - Health Science Center Graduate Program in Anesthesia Nursing. She is currently assigned to Walter Reed Army Medical Center for the clinical phase of the graduate program in anesthesia nursing. She will be stationed at Tripler Army Medical Center upon completion of the program.

Bradley Christian West was born in Knoxville, Tennessee on January 30, 1970, the son of Bill and Anna West. He graduated from Carter High School in Strawberry Plains, Tennessee in 1988. He received a Bachelor of Science in Nursing from Carson-Newman College in Jefferson City, Tennessee and was commissioned in the United States Army in May of 1992. His first duty assignment was in El Paso, Texas at William Beaumont Army Medical Center. He then attended the Intensive Care Nursing Course at Fort Sam Houston, Texas and was designated the Distinguished Honor Graduate. He is currently enrolled in the U.S. Army / University of Texas Houston - Health Science Center Graduate Program in Anesthesia Nursing. He is currently assigned to Walter Reed Army Medical Center for the clinical phase of the graduate program in anesthesia nursing. He will be stationed at Madigan Army Medical Center upon completion of the program.